

REMARKS**Rejections Under 35 USC § 103**

Claims 22-28, 45, 49 and 51 are rejected over Gianelly in view of Kronenberg, Gardella and Sindrey and in further view of Yamasaki, Collins, Kamata Chao and Tam. Claims 22, 49 and 51 are rejected over Gianelly in view of Kronenberg, Gardella and Sindrey and in further view of Yamasaki, Collins, Kamata, Chao and Tam and in further view of Schluter. Applicants traverse this rejection on the grounds that the Examiner has failed to establish a *prima facie* case of obviousness.

Gianelly

Gianelly suggests the possibility of enhancing orthodontic tooth movement by the local use of PTH. The local use was effected by a single administration. Five days later, a force was applied to bring about tooth movement. As a result, "[a]long the alveolar bone of the distal aspect of the teeth subjected to force, bone resorption and partial disorganization of the fibers of the ligament were apparent."

On the other hand, in the present invention, PTH was administered continuously. As described in Example 1 of the present specification, in the continuously PTH-treated rats, no necrotic tissue was observed in the pressured side on day 3 of teeth separation. This result could not have been reasonably expected in light of the disclosure of Gianelly. Therefore, it is apparent that the present invention is completely different from that of Gianelly, from the viewpoint of the administration and effect of PTH. Thus, the present invention is not suggested by the teachings of Gianelly in view of any combination of the other references cited nor can Gianelly with any of combination of references form a basis for a reasonable expectation of success.

Chao, Tam, and Kamata

The Examiner alleges that one of ordinary skill in the art would be motivated to modify the teachings disclosed in Chao and Tam to continuously administer PTH. Chao suggests that using prostaglandin E₂ for activating alveolar bone resorption during orthodontic tooth

movement could achieve a more rapid bone modeling and tooth movement. On the other hand, Tam describes that continuous administration of PTH results in bone loss. -

However, applicants respectfully urge that the examiner's allegation has a serious misconception. That is, "bone loss" is not the same as "bone resorption." An increase in bone resorption is not synonymous with bone loss.

As recognized by the Examiner, it has been observed that intermittent administration of PTH increases bone volume, whereas continuous administration of PTH results in bone loss (see Tam).

On the other hand, the Tam reference establishes that unpredictability of field would not allow one to form a reasonable expectation of success. In column 1, lines 45-51, Tam states that "mechanisms controlling bone turnover are complex and are not well understood at this time," and "[t]he complexity of the control mechanisms has resulted in a variety of approaches to reducing bone loss." As is evidenced from the description, one of ordinary skill in the art would not have expected the mechanism of bone turnover.

Intermittent administration of PTH increases bone volume (Tam), whereas promotion of tooth movement by intermittent administration is a result of acceleration of the appearance of osteoclasts and bone resorption (Kamata).

Continuous administration of PTH results in bone loss (Tam); however, there is no description in Tam, or in any of the other cited references, such as Kamata and Gineally, with regard to whether continuous administration of PTH increases osteoclast activity.

As described above, the effects of PTH on bone volume are completely different, depending on whether continuous administration or intermittent administration is adopted. Therefore, it is not possible for one of ordinary skill in the art to have a reasonable expectation that osteoclast activity will be increased by continuous administration. Namely, it is not obvious to one of ordinary skill in the art that continuous administration of PTH increases tooth movement, even though bone volume is reduced under continuous administration. Bone loss under continuous administration may be the result of the reduction of bone formation rather than an increase of bone resorption.

In view of the foregoing, even though it may have been known that activation of alveolar bone resorption can achieve a more rapid tooth movement, it would not have been obvious to one of ordinary skill in the art to modify the teachings of the references in view of the teaching that continuous administration results in bone loss.

Collins

The Examiner cites from the Collins article “[t]hat although various orthodontic appliances may differ in their mode of action they all must ultimately achieve the same effect.” From the description, the examiner is likely to allege that either an increase in bone volume or bone loss would result in increased tooth movement. However, this allegation is improper. When it is the case that an effect is different, not an action, the end results must be different. ;

Therefore, it is considered that one of ordinary skill in the art would expect a different result from continuous administration which results in a different effect from intermittent administration when continuous administration is applied in light of the teachings disclosed in the cited references.

In addition, since mechanisms controlling bone turnover are complex (Tam), a combination of many teachings cannot simply lead to the end result. In this context, the effect of continuous administration as described in Example 2 of the present specification should be viewed as non-obvious.

Moreover, none of the other references cited by the Examiner remedy the deficiencies of the references discussed above. Therefore, applicants request withdrawal of the rejection of claims 22-28, 45, 49 and 51 because the Examiner has not established proper motivation to combine the references, nor a reasonable expectation of success in their combination.

With respect to the additional citation of Schluter against claims 22, 49 and 51, applicants contend that this reference discussing dosage units does not render the present invention obvious.

Conclusion

In view of the foregoing remarks, applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited. If there are any questions regarding the application, the Examiner is invited to contact the undersigned at the number below.

Respectfully submitted,

Date July 24, 2003

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